

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	302	(cerebral adj vascular adj disease)	USPAT	OR	OFF	2005/06/30 14:41
L2	717	(stroke or migraine or vasospasm or (head adj injury) or (brain adj injury)) near6 (blood adj flow)	USPAT	OR	OFF	2005/06/30 14:42
L3	25624	I1 or "I3"	USPAT	OR	OFF	2005/06/30 14:42
L4	1009	I1 or I2	USPAT	OR	OFF	2005/06/30 14:43
L5	0	I4 near10 HET0016	USPAT	OR	OFF	2005/06/30 14:43
L6	252	(HETE or (cytochrome adj P450 adj fatty adj acid adj omega adj hydroxylase)) near6 (inhibit or inhibitor or inhibition or inhibiting)	USPAT	OR	OFF	2005/06/30 14:56
L7	8	I6 and I4	USPAT	OR	OFF	2005/06/30 14:46

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	302	(cerebral adj vascular adj disease)	USPAT	OR	OFF	2005/06/30 14:41
L2	717	(stroke or migraine or vasospasm or (head adj injury) or (brain adj injury)) near6 (blood adj flow)	USPAT	OR	OFF	2005/06/30 15:09
L3	25624	I1 or "I3"	USPAT	OR	OFF	2005/06/30 14:42
L4	1009	I1 or I2	USPAT	OR	OFF	2005/06/30 14:43
L5	0	I4 near10 HET0016	USPAT	OR	OFF	2005/06/30 14:43
L6	252	(HETE or (cytochrome adj P450 adj fatty adj acid adj omega adj hydroxylase)) near6 (inhibit or inhibitor or inhibition or inhibiting)	USPAT	OR	OFF	2005/06/30 14:56
L7	8	I6 and I4	USPAT	OR	OFF	2005/06/30 14:46
L8	160149	(stroke or migraine or vasospasm or (head adj injury) or (brain adj injury))	USPAT	OR	OFF	2005/06/30 15:09
L9	160268	L1 or L8	USPAT	OR	OFF	2005/06/30 15:09
L10	0	L9 near10 HET0016	USPAT	OR	OFF	2005/06/30 15:10
L11	52	L6 and L8	USPAT	OR	OFF	2005/06/30 15:11
L12	0	L11 and HET0016	USPAT	OR	OFF	2005/06/30 15:11

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L1 476195 (CEREBRAL VASCULAR DISEASE) OR STROKE OR MIGRAINE OR
 VASOSPASM
 OR (HEAD INJURY) OR (BRAIN INJURY) OR ALZHEIMER'S OR
 DEMENTIA
 OR PARKINSON'S OR HUNTINGTON

=> s l1 (10A) HET0016
 L2 1 L1 (10A) HET0016

=> d l2 bib ab

L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
 AN 2002:353270 CAPLUS
 DN 136:363861
 TI Use of 20-HETE synthesizing enzyme inhibitors as therapy for
 cerebral
 vascular diseases
 IN Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato,
 Masakazu;
 Kameo, Kazuya; Okuyama, Shigeru
 PA MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co.,
 Ltd.
 SO PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.
WO 2002036108	A2	20020510	WO 2001-US27605
20010906			
WO 2002036108	A3	20021017	
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,			
CH, CN,			
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,			
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,			
LK, LR,			
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BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,			
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CA 2427557	AA	20020510	CA 2001-2427557
20010906			
AU 2001088798	A5	20020515	AU 2001-88798
20010906			
EP 1330240	A2	20030730	EP 2001-968558
20010906			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE,
MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004512361	T2	20040422	JP 2002-538920
20010906			

PRAI US 2000-245638P	P	20001103
WO 2001-US27605	W	20010906

AB A method for treating cerebral vascular diseases in a human or non-human animal is disclosed. The method involves inhibiting 20-HETE synthesizing enzyme activity sufficiently to increase or prevent a decrease in cerebral blood flow in the human or non-human animal.

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 Parkinson's or Huntington

L1 476195 (CEREBRAL VASCULAR DISEASE) OR STROKE OR MIGRAINE OR
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OR (HEAD INJURY) OR (BRAIN INJURY) OR ALZHEIMER'S OR
DEMENTIA
OR PARKINSON'S OR HUNTINGTON

=> s l1 (10A) HET0016
L2 1 L1 (10A) HET0016

=> d l2 bib ab

L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:353270 CAPLUS
DN 136:363861
TI Use of 20-HETE synthesizing enzyme inhibitors as therapy for
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IN Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato,
Masakazu;
Kameo, Kazuya; Okuyama, Shigeru
PA MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co.,
Ltd.
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.
DATE	-----	----	-----	-----

PI	WO 2002036108	A2	20020510	WO 2001-US27605
	20010906			
	WO 2002036108	A3	20021017	
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,			
CH, CN,	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,			
GE, GH,	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,			
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TR, BF,	BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,			
TG				

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20010906			
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20010906			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004512361	T2	20040422	JP 2002-538920
20010906			

PRAI US 2000-245638P	P	20001103
WO 2001-US27605	W	20010906

AB A method for treating cerebral vascular diseases in a human or non-human animal is disclosed. The method involves inhibiting 20-HETE synthesizing enzyme activity sufficiently to increase or prevent a decrease in cerebral blood flow in the human or non-human animal.

=> s (20-HETE or (cytochrome P450 fatty acid omega hydroxylase)) (6A)
(inhibit or inhibitor or inhibition or inhibiting)
L3 351 (20-HETE OR (CYTOCHROME P450 FATTY ACID OMEGA HYDROXYLASE))
(6A) (INHIBIT OR INHIBITOR OR INHIBITION OR INHIBITING)

=> s l1 and l3
L4 9 L1 AND L3

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L5 8 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)

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L6 4 L1 AND HET0016

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L7 4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)

=> s l6 or l5

L8 8 L6 OR L5

=> d 18 1-8 bib ab

L8 ANSWER 1 OF 8 MEDLINE on STN
AN 2004532827 MEDLINE
DN PubMed ID: 15503650
TI Mechanisms regulating cerebral blood flow as therapeutic
 targets.
AU Pratt Phillip F; Medhora Meetha; Harder David R
CS Cardiovascular Center, Department of Pharmacology and
 Toxicology, Medical
 College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI
 53226,
 USA.. ppratt@mcw.edu
NC HL-069996 (NHLBI)
 HL-33833 (NHLBI)
 HL-59996 (NHLBI)
 HL-68769 (NHLBI)
SO Current opinion in investigational drugs (London, England :
 2000), (2004
 Sep) 5 (9) 952-6. Ref: 34
 Journal code: 100965718. ISSN: 1472-4472.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200501
ED Entered STN: 20041027
 Last Updated on STN: 20050126
 Entered Medline: 20050125
AB Regulation of cerebral blood flow (CBF) is critical for the
 maintenance of
 neural function and hence survival of the organism. Since the
 brain does
 not store glycogen, unlike muscle, a constant supply of glucose
 and oxygen
 are needed for the minute-by-minute demands of cerebral
 function. This
 review focuses on important lipid mediators that act as
 reciprocal
 regulators of cerebral artery diameter and their potential as
 targets for
 therapeutic intervention in diseases such as ischemia, **stroke**
 and subarachnoid hemorrhage. Cytochrome P450 metabolism of
 arachidonic
 acid to 20-hydroxyeicosatetraenoic acid (20-HETE) or
 epoxyeicosatrienoic
 acids (EETs) provides a mechanism for the constriction and
 relaxation of

cerebral arteries, respectively. Additionally, EETs have mitogenic potential and may contribute to angiogenesis in the brain, which has important implications during recovery from cerebral injury. Finally, we discuss novel **inhibitors** of 20-HETE formation and actions as well as interventions to enhance EET production in cerebrovascular disease.

L8 ANSWER 2 OF 8 MEDLINE on STN

AN 2003209741 MEDLINE

DN PubMed ID: 12677022

TI Contribution of 5-hydroxytryptamine_{1B} receptors and 20-hydroxyeicosatetraenoic acid to fall in cerebral blood flow after subarachnoid hemorrhage.

AU Cambj-Sapunar Liana; Yu Ming; Harder David R; Roman Richard J

CS Department of Physiology, Medical College of Wisconsin, 8701 Watertown

Plank Rd, Milwaukee, WI 53226, USA.

SO Stroke; a journal of cerebral circulation, (2003 May) 34 (5) 1269-75.

Electronic Publication: 2003-04-03.

Journal code: 0235266. ISSN: 1524-4628.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200306

ED Entered STN: 20030506

Last Updated on STN: 20030701

Entered Medline: 20030630

AB BACKGROUND AND PURPOSE: This study examined the interaction between

5-hydroxytryptamine_{1B} (5-HT_{1B}) receptors and

20-hydroxyeicosatetraenoic

acid (20-HETE) in contributing to the acute fall in regional cerebral

blood flow (rCBF) after subarachnoid hemorrhage (SAH) in rats.

METHODS:

The effects of intracisternal injection of 0.3 mL of arterial blood,

artificial cerebrospinal fluid, and 5-HT on rCBF and the levels of 20-HETE

and 5-HT in cerebrospinal fluid were measured in rats pretreated with

vehicle, a 5-HT_{1B} receptor antagonist (isamoltane hemifumarate), or an

inhibitor of the synthesis of 20-HETE (

HET0016). The effects of **HET0016** and isamoltane on the

vasoconstrictor response and changes in $[Ca^{2+}]_i$ to 5-HT were also studied in middle cerebral arteries and vascular smooth muscle cells isolated from these vessels. RESULTS: 20-HETE and 5-HT levels in cerebrospinal fluid rose from 172 ± 10 to 629 ± 44 ng/mL and from 6 ± 4 to 1163 ± 200 nmol/mL, respectively, after SAH. rCBF fell by 30% 10 minutes after SAH, and it remained at this level for the next 2 hours. Blockade of 5-HT_{1B} receptors prevented the sustained fall in rCBF seen after SAH. Intracisternal injection of 5-HT mimicked SAH by increasing 20-HETE levels in cerebrospinal fluid to 475 ± 94 ng/mL and reducing rCBF by 30%. Blockade of the synthesis of 20-HETE with **HET0016** prevented the fall in rCBF produced by 5-HT. Isamoltane and **HET0016** reduced the vasoconstrictor response of isolated MCA to 5-HT by >60% and diminished the rise in $[Ca^{2+}]_i$ produced by 5-HT in vascular smooth muscle cells isolated from these arteries. CONCLUSIONS: These results suggest that the release of 5-HT after SAH activates 5-HT_{1B} receptors and the synthesis of 20-HETE and that 20-HETE contributes to the acute fall in rCBF by potentiating the vasoconstrictor response of cerebral vessels to 5-HT.

L8 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 2004:204096 BIOSIS

DN PREV200400204639

TI Reduction of brain damage following focal cerebral ischemia by

TS - 011, a

20 - hydroxyeicosatetraenoic acid synthesizing enzyme inhibitor.

AU Omura, T. [Reprint Author]; Miyata, N. [Reprint Author]; Tanaka, Y.

[Reprint Author]; Kitano, K. [Reprint Author]; Koizumi, C.

[Reprint

Author]; Fukawasa, M. [Reprint Author]; Endo, H. [Reprint Author];

Hachiuma, K. [Reprint Author]; Minagawa, T. [Reprint Author]; Sakurai, T.

[Reprint Author]; Yoshida, S. [Reprint Author]; Okuyama, S.

[Reprint

Author]; Nakaike, S. [Reprint Author]; Roman, R. J.; Harder, D.

R.

CS Dept of Physiology, Taisho Pharmaceut. Co., Ltd, Saitama, Japan

SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003)

Vol. 2003, pp. Abstract No. 741.5. <http://sfn.scholarone.com>.
e-file.

Meeting Info.: 33rd Annual Meeting of the Society of
Neuroscience. New
Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 14 Apr 2004

Last Updated on STN: 14 Apr 2004

AB 20-Hydroxyeicosatetraenoic acid (20-HETE) is one of the
metabolites of

arachidonic acid catalyzed by CYP4A isozymes. **20-HETE**
inhibits the large-conductance, Ca²⁺-activated K⁺-channel and
increases Ca²⁺ influx through the voltage-gated Ca²⁺ channel.

20-HETE

potently constricts cerebral arteries from a variety of species
through

these mechanisms. Recent studies have indicated that 20-HETE
contributes

the acute fall in cerebral blood flow in rats following
subarachnoid

hemorrhage. **Inhibition** of **20-HETE** formation

might increase collateral blood flow and be useful in reducing
brain

damage following ischemic **stroke** as well. Recently, we
developed the potent and selective **inhibitor** of **20-**

HETE synthesizing enzyme, TS-011. The present study examined the
effects of TS-011 on infarct size following 1 hr of transient
occlusion

and 23 hr of reperfusion of the middle cerebral artery occlusion
(MCAO) of

rats. Plasma levels of 20-HETE increased significantly from 518
to 772

pg/mL 3 and 6 hours after occlusion and reperfusion of MCA.

There was also

upregulation of the expression of CYP4A protein in the penumbra
region of

infarct area in comparison to the contralateral hemisphere.

Intravenous

infusion of TS-011 (0.1 mg/kg/hr) significantly reduced the
infarct volume

by 35%. The reduction of infarct volume by TS-011 was even
observed when

the compound was administered 4 hours after occlusion of the
MCA. TS-011

prevented the increase in plasma 20-HETE levels following
occlusion and

reperfusion of the MCA. TS-011 also reduced the infarct volume
by 30 % in

a photochemically-induced model of permanent MCAO of rats.

These results

suggest that **inhibition** of the production of 20-**HETE** with TS-011 provides neuroprotection following ischemic **stroke**.

L8 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 2003:89980 BIOSIS

DN PREV200300089980

TI An **Inhibitor** of 20-**HETE** Formation Attenuates the Fall in Cerebral Blood Flow Following Subarachnoid Hemorrhage.

AU Okamoto, Hirotsugu [Reprint Author]; Maier, Kristopher G. [Reprint

Author]; Harder, David R. [Reprint Author]; Roman, Richard J.

[Reprint

Author]

CS Physiology, Medical College of Wisconsin, Milwaukee, WI, USA

SO Anesthesiology Abstracts of Scientific Papers Annual Meeting, (2002) No.

2000, pp. Abstract No. 736. <http://www.asa-abstracts.com>.

cd-rom.

Meeting Info.: 2000 Annual Meeting of the American Society of Anesthesiologists. San Francisco, CA, USA. October 16-18, 2000.

American

Society of Anesthesiologists Inc.

DT Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 12 Feb 2003

Last Updated on STN: 12 Feb 2003

AB INTRODUCTION: Acute cerebral **vasospasm** following subarachnoid hemorrhage (SAH) causes ischemic **stroke**. Although endothelin, nitric oxide and thromboxane have been implicated to play a role in

cerebral **vasospasm**, the relative importance of these mediators versus others have not been fully resolved. Recently, a

cytochrome P450

metabolite of arachidonic acid, 20-hydroxyeicosatetraenoic acid (20-**HETE**) (a potent vasoconstrictor), has been reported to play a

pivotal

role in the regulation of cerebrovascular tone. To examine the

role of

20-**HETE** in mediating acute cerebral **vasospasm**, we compared

cerebral blood flow responses following SAH in rats treated with

vehicle

or an **inhibitor** of 20-**HETE**

formation, 17-ODYA. METHODS: Experiments were performed on

ketamine and

thiobutabarbital anesthetized male Sprague-Dawley rats

weighing 250-300

g. The animals were artificially ventilated and arterial

pressure and

PCO2 levels were monitored. Regional cerebral blood flow (rCBF) was

continuously measured with laser-Doppler flowmetry through thin closed

cranial window over the parietal region of the cerebral cortex. SAH was

induced by injecting 0.3 ml of arterial blood into the Cisterna Magna.

20-HETE levels were measured by fluorescent HPLC from samples drawn via

Cisterna Magna before and after SAH. Rats were divided into two groups.

In group 1 (n=7), rats were given an injection of 2 nmoles of 17-ODYA into

the Cisterna Magna 1 hour prior to SAH. In group 2 (n=5), rats received

vehicle. Data was expressed mean \pm SEM and significance of differences

was determined using ANOVA followed by a Duncan's test.

RESULTS: In

vehicle-treated rats, rCBF fell by 40% within 10 minutes after SAH, and it

remained at this level for the 2 hour duration of the experiment. In

contrast, the initial decrease in rCBF was significantly less in the rats

pretreated with 17-ODYA, and rCBF returned to pre-SAH levels within 2

hours (See Figure). In vehicle-treated rats, 20-HETE levels in cerebrospinal fluid (CSF) increased significantly from 7.5 \pm 4 ng/ml to

204 \pm 13 ng/ml after injection of blood; while 20-HETE levels did not

increase in the 17-ODYA treated rats. CONCLUSIONS: These results indicate

that SAH markedly increased 20-HETE levels in CSF, and 17-ODYA prevented

both the increase of 20-HETE levels and the fall in rCBF following SAH.

20-HETE, a cytochrome P450 metabolite of arachidonic acid, may contribute

to acute cerebral **vasospasm** following SAH. Preventing the production of, or the actions of 20-HETE, after SAH may provide a new

therapeutic approach for the treatment of SAH and cerebral **vasospasm**.

L8 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 2002:271687 BIOSIS

DN PREV200200271687

TI 20-HETE contributes to the acute fall in cerebral blood flow after

subarachnoid hemorrhage in the rat.

AU Kehl, Franz; Cambj-Sapunar, Liana; Maier, Kristopher G.; Miyata, Noriyuki;

Kametani, Shunishi; Okamoto, Hirotsugu; Hudetz, Anthony G.; Schulte, Marie

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SO American Journal of Physiology, (April, 2002) Vol. 282, No. 4
Part 2, pp.

H1556-H1565. print.

CODEN: AJPHAP. ISSN: 0002-9513.

DT Article

LA English

ED Entered STN: 1 May 2002

Last Updated on STN: 1 May 2002

AB This study examined the effects of blocking the formation of
20-hydroxyeicosatetraenoic acid (20-HETE) on the acute fall in
cerebral

blood flow after subarachnoid hemorrhage (SAH) in the rat. In
vehicle-treated rats, regional cerebral blood flow (rCBF)
measured with

laser-Doppler flowmetry fell by 30% 10 min after the injection
of 0.3 ml

of arterial blood into the cisterna magna, and it remained at
this level

for 2 h. Pretreatment with **inhibitors** of the formation of
20-HETE, 17-octadecynoic acid (17-ODYA; 1.5 nmol
intrathecally) and

N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine (
HET0016; 10 mg/kg iv), reduced the initial fall in rCBF by 40%,
and rCBF fully recovered 1 h after induction of SAH. The
concentration of

20-HETE in the cerebrospinal fluid rose from 12+-2 to 199+-17
ng/ml after

SAH in vehicle-treated rats. 20-HETE levels averaged only 15+-11
and

39+-13 ng/ml in rats pretreated with 17-ODYA or **HET0016**,
respectively. **HET0016** selectively inhibited the formation of
20-HETE in rat renal microsomes with an IC50 of <15 nM and human
recombinant CYP4A11, CYP4F2, and CYP4F3 enzymes with an IC50 of
42, 125,

and 100 nM, respectively. These results indicate that 20-HETE
contributes

to the acute fall in rCBF after SAH in rats.

L8 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson
Corporation on STN

AN 2001:252340 BIOSIS

DN PREV200100252340

TI Blockade of 20-HETE formation attenuates cerebral **vasospasm** after subarachnoid hemorrhage in the rat.

AU Kehl, Franz [Reprint author]; Okamoto, Hirotsugu [Reprint author]; Maier, Kristopher G. [Reprint author]; Miyata, Noriyuki; Kametani, Shunishi; Harder, David R. [Reprint author]; Roman, Richard J. [Reprint author]

CS Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA

SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A127. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001. CODEN: FAJOEC. ISSN: 0892-6638.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB Previous studies have reported that the formation of vasoconstrictor metabolites of arachidonic acid (AA) following subarachnoid hemorrhage (SAH) is elevated. Since the primary metabolite of AA in the cerebral circulation is 20-hydroxyeicosatetraenoic acid (20-HETE), the present study examined its role in the development of cerebral **vasospasm** following SAH in the rat. Regional cerebral blood flow (rCBF) was measured using laser Doppler flowmetry. SAH was induced by injection of 0.3 ml autologous arterial blood into the Cisterna Magna of rats that were pretreated with vehicle, a **20-HETE** and EET **inhibitor** 17-octadecynoic acid (17-ODYA) (1.5 nM, intrathecally), or a selective **inhibitor** of **20-HETE** formation, N-hydroxy-N'-(4-butyl-2-methylphenyl)-formamidine (**HET0016**) (10 mg/kg, i.v.). Cerebrospinal fluid (CSF) was collected before and after SAH and the effects of **HET0016** on the formation of 20-HETE in rat renal cortical microsomes were determined. In control rats, rCBF fell 30% 10 min after the induction of SAH and remained at this level for the 2 hr duration of the experiment. Pretreatment of the rats with 17-ODYA or **HET0016** reduced the initial fall in

rCBF at 10 min by 40% and rCBF fully recovered to control values
90 min
after induction of SAH. The 20-HETE concentration in CSF
averaged 180+-10
ng/ml after SAH in control animals and only 15+-5 and 60+-10
ng/ml in rats
treated with 17-ODYA or **HET0016**. **HET0016** selectively
inhibited the formation of 20-HETE by renal microsomes with an
IC50 of 15
nM. It had no effect on epoxxygenase activity even at a
concentration of
1000 nM. The results of the present study indicate that the
levels of
20-HETE are elevated in CSF following SAH and that CYP4A
inhibitors are
effective in preventing the **vasospasm** in rats in vivo and have
potential as therapeutic agents.

L8 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:147800 CAPLUS

DN 140:399863

TI Effects of a 20-HETE antagonist and agonists on cerebral
vascular tone

AU Yu, Ming; Cambj-Sapunar, Liana; Kehl, Franz; Maier, Kristopher
G.;

Takeuchi, Kazuhiko; Miyata, Noriyuki; Ishimoto, Tsuyoshi; Reddy,
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Manmohan; Falck, John R.; Gebremedhin, Debebe; Harder, David R.;
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SO European Journal of Pharmacology (2004), 486(3), 297-306
CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier Science B.V.

DT Journal

LA English

AB This study examined the effects of a 20-hydroxyeicosatetraenoic
acid

(20-HETE) antagonist, 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid
(WIT002)

and two agonists,
4-amino-N-(20-hydroxy-eicosa-5(Z),14(Z)-dienoyl)

benzenesulfonamide (ABSA) and
20-hydroxyeicosa-5(Z),14(Z)-dienoic acid

(WIT003), on the diameter of rat middle cerebral arteries in
vitro and on

cerebral blood flow in vivo. WIT003, ABSA and 20-HETE all had a
similar

effect to reduce the diameter of the middle cerebral artery by
26%. WIT003

and 20-HETE both increased intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) in vascular smooth muscle cells isolated from the middle cerebral artery. In contrast, WIT002 had no effect on the basal diameter of the middle cerebral artery but it attenuated the vasoconstrictor responses and the rise in $[\text{Ca}^{2+}]_i$ in vascular smooth muscle cells following administration of 20-HETE and 5-hydroxytryptamine (5-HT). WIT003 partially restored the vasoconstrictor response to 5-HT in the middle cerebral artery after administration of an **inhibitor** of the endogenous synthesis of **20-HETE**. Infusion of the 20-HETE agonists, WIT003 and ABSA, into cisterna magna of rats reduced baseline cerebral blood flow by 20%, whereas administration of the 20-HETE antagonist, WIT002, had no effect. Intracisternal injection of WIT002 attenuated the fall in cerebral blood flow following injection of blood into the cisterna magna, whereas administration of the 20-HETE agonist, ABSA, potentiated this response. These findings indicate that the 20-HETE agonists, WIT003 and ABSA, increase cerebral vascular tone both in vivo and in vitro and suggest blocking the vasoconstrictor actions of 20-HETE may be useful to prevent the acute fall in cerebral blood flow following subarachnoid hemorrhage.

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:353270 CAPLUS
DN 136:363861
TI Use of **20-HETE** synthesizing enzyme **inhibitors**
as therapy for **cerebral vascular diseases**
IN Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato,
Masakazu;
Kameo, Kazuya; Okuyama, Shigeru
PA MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co.,
Ltd.
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.
DATE			
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PI WO 2002036108	A2	20020510	WO 2001-US27605
20010906			
WO 2002036108	A3	20021017	
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2427557	AA	20020510	CA 2001-2427557
20010906			
AU 2001088798	A5	20020515	AU 2001-88798
20010906			
EP 1330240	A2	20030730	EP 2001-968558
20010906			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2004512361	T2	20040422	JP 2002-538920
20010906			
PRAI US 2000-245638P	P	20001103	
WO 2001-US27605	W	20010906	
AB			
A method for treating cerebral vascular diseases in a human or non-human animal is disclosed. The method involves inhibiting 20-HETE synthesizing enzyme activity sufficiently to increase or prevent a decrease in cerebral blood flow in the human or non-human animal.			